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TITLE: The Treatment of BRCA1/2 Hereditary BRCA1/2 and Sporadic Breast Cancer
with Poly(ADP-Ribose) Polymerase Inhibitors and Chemotherapy

PRINCIPAL INVESTIGATOR: Joseph A. De Soto M.D., Ph.D.

CONTRACTING ORGANIZATION: The Henry M. Jackson Foundation for the
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14. ABSTRACT Each year there are over 200,000 new cases of breast cancer in the U.S. alone. Current chemotherapeutic therapies are highly toxic and relatively non-specific. BRCA1 and BRCA2 hereditary breast cancers are responsible of the about 10% of the breast cancer cases. In is addition it is unknown whether current therapies adequately address differences between BRCA1 hereditary and sporadic breast cancers. In this study, we look at a new class of anti-cancer drugs called PARP-1 inhibitors that inhibit the repair of damaged DNA. These drugs may be useful alone or in combination with standard chemotherapy in the treatment of breast cancer due to the inherent genetic instability of most breast cancer cells. Here, we show a difference in sensitivity to PARP1 inhibitors by different breast cancer types and and enhancement of the cytotoxicity of standard chemotherapy without an addition to toxicityThis data may set the basis for future clinical trials.					
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Table of Contents

Introduction	6
Body	6
Key Research Accomplishments	9
Reportable Outcomes	9
Conclusion	10
References	11
Appendices	12

Introduction:

This project seeks to address the ability of Poly(ADP)ribose polymerase inhibitors to inhibit both sporadic and BRCA1/ 2 hereditary breast cancer alone and in combination with standard chemotherapy regimens.

PARP-1 inhibitors inhibit the ability of cells to repair damaged DNA, most cancer cells by their nature have deficits in their ability to repair damaged DNA. BRCA1 and 2 breast cancers are particularly deficient in their ability to repair damaged DNA.

In this project, multiple breast cancer cell lines are screened against PARP inhibitors alone and in combination with over 100 different chemotherapeutic agents. The therapeutic approaches that show the most promise are further screened in animal grafts where the toxicity of the therapy will also be evaluated.

Body:**Task 1: Dose Response Curves**

Dose response curves were generated using the PARP1 inhibitor AG14361 against 20 human breast cancer cell lines alone in vitro. It was found that BRCA2 breast cancer cell lines were the most sensitive to PARP1 inhibition. BRCA1 cell lines and those with deficits in homologous repair (HR) were next in sensitivity to inhibition alone by PARP inhibitors (other than BRCA2 mutation) . Finally sporadic breast cancer were inhibited by PARP1 inhibitors but with slightly less activity than that of BRCA1 or those with homologous repair defect.

Sensitivity of Human Breast cancer to PARP1 inhibition from greatest to least:

BRCA2 >> BRCA1 or HR > Sporadic

It was found that low doses of PARP1 inhibitor actually increased breast cancer cellular growth

The breast cancer cell lines were then tested in combination with over 100 chemotherapeutic agents. The following was found by drug class:

Parp1 inhibitors enhance the ability of alkylating agents, topoisomerase II inhibitors and platinum like agents in inhibiting breast cancer cell growth.

PARP I inhibitors showed a mixed effect with anti-mitotics. In some cases PARP 1 inhibitors enhanced the ability of antimetabolites to inhibit breast cancer growth at other times they enhanced the ability. Unsure of mechanism.

PARP inhibitors antagonized the ability of antimetabolites to inhibit breast cancer growth. Exception, 5-FU is enhanced. 5-FU it is found also induces SS breaks.

Natural products with PARP inhibitor are now being evaluated.

Task II: In vitro treatment of BRCA mouse tumor cell lines implanted into nude mice to form allografts:

Results mimic those from Task I in terms of the ability of PARP1 inhibitor alone or in combination with standard chemotherapy to inhibit mammary tumor growth.

BRCA2 mammary tumor cell lines are much more sensitive to inhibition than BRCA1, HR or sporadic breast cancers.

Note: In retrospect, Task II may not have been necessary as relevance to human cancer trumped by task III while Task II provided preliminary data in order to complete both task II and Task III

Task III: In vitro treatment of human /mouse breast cancer BRCA xenografts

Results mimic the in vitro results by both single agent and in combination with standard chemotherapy. BRCA1 and HR breast cancer cells are slightly more sensitive to PARP1 inhibition than sporadic breast cancer. Enhancement seen with alkylating agents, platinum type agents, 5-FU, topoisomerase inhibitors. Taxanes with PARP inhibitor give mixed results.

Human breast cancer tissue is much less sensitive to both PARP1 inhibition, standard chemotherapy and combinational therapy.

Necropsy of mice does not show enhancement of toxicities. Debatable evidence of protection against toxicity.

Task IV: Ability of PARP1 inhibitors to prevent the development of hereditary BRCA mammary tumors in MMTV-p53 mice.

BRCA co/co . MMTV – p53 mice all developed mammary tumors by age of 13 months when not treated. PARP1 inhibited the formation of mammary tumors in mice. Results:

Mice treated from 3 months to 1 year - 3 month with either placebo or PARP-1 inhibitor 15 mg/kg per day/

	Survived	Number with tumors by 13 months
Control 10 mice	9	9
Treated 10 mice	8	0

In the control group 1 mouse died to probable infection. In the treated group 1 mouse died from infection another died from unknown causes. PARP1 inhibitors seems to inhibit the development of mammary tumors in mice. Sample size still to small? Must increase number of mice?

Task V: Presentations and Publications of Work

Presentations have gone exceptionally well, including a presentation at the World Cancer Conference. Publications have been delayed due to having to replicate much of the work. A post-doc was found to have falsified his data. He was terminated. Thus, 6 months of research was lost and all his work had to be redone. A Full stop was placed on publications. Presentations were amended to include work that he was not involved in.

Summation, TASK I is complete, TASK II is complete, Task III nearly complete, Task 4 in progress, Task 5 in progress. It is noted that in retrospect Task II may have not been necessary.

Other research impacting this project: A phase I trial evaluating the PARP1/2 inhibitor AZD2281 against BRCA1, BRCA2, and sporadic breast & Ovarian cancer was recently published by Fu et al. in the NEJM. In this report, less than 50% of the BRCA1 and BRCA2 breast cancer showed response while none of the sporadic breast cancer showed a response. The BRCA2 cancers were more sensitive to PARP inhibition alone than BRCA1 cancer. The results for are consistent with ours except that in vitro we also show the ability of PARP1 inhibitors to slow the rate of growth of sporadic tumor cells. At ASCO 2009 it was reported that the PARP inhibitor BSI-201 double the overall progression free survival when used in combination with gemcitabine/carboplatin against triple negative breast cancer in a phase II study giving preliminary results O'Shaunessy et al. The enhancement of activity was seen in this report was consistent with our results. About 1/3 of triple negative breast cancers are BRCA deficient.

Key Research Accomplishments:

- Triple Negative Breast cancer also susceptible to PARP inhibitors
- BRCA1 mammary cancer prevented by PARP-1 inhibitors
- Breast cancer with defects in Homologous repair sensitive to PARP-1 inhibitors
- BRCA2 cancers more highly sensitive to PARP1 inhibition than BRCA2
- Enhancement/Synergy with standard chemotherapy
- 5-FU a well known antimetabolite also induces single strand breaks
- PARP1 inhibitor in vitro are more potent than PARP1/2 inhibitors

Reportable Outcomes:

Abstracts:

De Soto JA, The use of Poly(ADP-ribose) polymerase inhibitors in the treatment of cancer, Proceeding of the World Cancer Congress, Beijing, China pg 478 June 22-24, 2009.

De Soto JA, Reconsidering Anthracycline Based Chemotherapy in the Treatment of Breast Cancer in African American Women. Journal of the National Medical Association 2008 (July 24, 2008).

Presentations:

De Soto JA, The use of Poly(ADP-ribose) polymerase inhibitors in the treatment of cancer, World Cancer Congress, Beijing, China. June 23 2009.*

De Soto JA, The use of Poly(ADP-ribose) polymerase inhibitors in the treatment of Ovarian and Breast cancer. USUHS Research Week. May 14 2008.

De Soto JA, The use of standard chemotherapy with poly(ADP-ribose)polymerase (PARP1) inhibitors in the treatment of hereditary breast cancer. The leading innovation and knowledge sharing meeting, BCRP meeting. Vienna, VA. Feb 10, 2009.

Cell Lines: Two new BRCA2 Breast cancer cell lines have been developed.

Grants: 1) An RO1 is in the process of being submitted based from the data developed from this project.

2) Clinical trial proposed and submitted based on the data developed under this grant

Jobs: I was offered two separate jobs at the level of Associate Professor 1) University of Texas 2) Howard University.

Conclusions : PARP1 inhibitors enhance the cytotoxicity of topoisomerase inhibitors, alkylating agents, platinum type agents, towards breast cancer cell lines. Used alone PARP1 inhibitors show greatest efficacy against BRCA2 hereditary breast cancer cells, followed by BRCA1 breast cancer and breast cancer with defects in homologous recombination. Animal studies thus far give similar results as found in the in vitro

studies, additionally there seems to be little to no toxicity from PARP1 inhibition as determined by necroscopy of nude mice.

If I had to re-write this grant , TASK2 looking at mouse to mouse allografts of mammary tumors would have been omitted as it took a lot of time without adding much to the results. In addition, making the transition from Post-doc to P.I. was much more difficult than I imagined, with time being used up not only by experimentation but by paperwork, administration, ordering, record keeping to the supervision of others. The experience of supervising others led to a change in my approach from a monthly analysis of employee activities to daily /weekly. In addition , if I could go back in time I would immediately acquired an assistant to deal with some of the busy work.

References:

Fong PC, Boss DS, Yap TA. Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers, N Engl J Med 2009;361:123-34.

O' Shaughnessy, Pippen J, Yoffe D, Efficacy of BSI-201 in combination with gecitabine/carboplatin in pateints with triple negative breast cancer. Results in a phase II trial. J Clin Oncolo 27:18s, 2009 9suppl;abstract 3)

Appendices: **CURRICULUM VITAE**

JOSEPH ANGEL DE SOTO, III

M.D., Ph.D., F.A.I.C.

**Graduate School of Nursing
Uniformed Services University of the
Health Sciences**

Education:

Institution/Location/Area of Concentration		
Year	Degree	
Dec 2005	Ph.D.	Pharmacology , Department of Pharmacology, Howard University Graduate School,

Year	Degree	Institution/Location/Area of Concentration
		Washington, DC
May 2005	M.D.	Medicine , Howard University College of Medicine, Washington, DC
June 1995	B.S.	Biophysical Chemistry , Department of Chemistry, La Sierra University

Professional Experience: (Civilian and Military experience)

Year	Position title/Institution/Duty Station/Location	Scope of Role
2007-present	Assistant Professor & Principal Investigator, Director Laboratory of Experimental Therapeutics, Pharmacogenomics and Cancer Pharmacology, Department of Health, Injury, and Disease Management, Graduate School of Nursing Uniformed Services University of the Health Sciences, Bethesda, MD	Course coordinator for pathology and Pharmacology. Basic and PhD faculty member. P.I. for the Laboratory of Experimental Therapeutics, Pharmacogenomics and Cancer Pharmacology
2005-2007	IRTA Post-Doctoral Fellow – Translational Research in Clinical Oncology. National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD	Research at NIH was in the area of experimental therapeutics, cancer chemotherapy, diabetes, and translational research. Designed experiments utilizing chemistry, toxicology, pharmacology, and molecular

Year	Position title/Institution/Duty Station/Location	Scope of Role
		biology. Carried out experiments, wrote papers, reviews, and grants. Presented papers orally at National meetings. Carried out statistical analysis. Evaluated basic research for use in the clinic. Carried out research with practical and relevant clinical applications.
2005-present	Adjunct Assistant Professor, Health, Pathopharmacology & Infectious Disease, Mountain State University, WV	Taught courses in microbiology/ infectious disease, anatomy, physiology, pathophysiology, and pathopharmacology. Determined materials to be covered, developed the syllabus, established criteria for grading, established tutorials, and counseled the students. Students included graduate, professional, pre-professional, and undergraduates. 20 courses taught.
2005-present	Medical Columnist, The Journal Newspaper, Martinsburg, WV	Write a monthly medical column on health issues of interest to the community. Topics covered include: infectious, genetic, developmental, and psychiatric disorders. Cancer, pathology, social issues, and healthcare are also covered. Respond to questions from the community and guidance to solve individual health care concerns.
2002-2005	Pharmacology Instructor, Howard University College of Medicine, Washington, D.C.	Taught pharmacokinetics, pharmacodynamics, molecular biology, toxicology, chemotherapy, statistical applications, antimicrobials, and endocrinology to doctoral students and professional (P.A.

Year	Position title/Institution/Duty Station/Location	Scope of Role
		and Medical) students.
1995-1997	Biochemistry Lab Instructor, La Sierra University, Riverside, CA	Instructed biochemical laboratory techniques to undergraduate students. Added in the development of laboratory curricula.
1992-1995	Research Assistant, La Sierra University, Riverside, CA	Molecular modeling, statistical analysis, computational chemistry, quantitative and qualitative analysis, and theoretical chemistry.
1990-1992	Nurse, Acute and Convalescent Nursing Care at Various Hospitals and Nursing Homes for an Agency	
1988-1989	Honorable Discharge Combat Medic, U.S. Army	Emergent healthcare of soldiers.

Honors and Awards: (Include Military, Educational, Professional)

2009	Invited Speaker	World Cancer Congress, Beijing, China
2009	Distinguished Civilian Faculty Award	GSN/Uniformed services University of the Health Sciences
2008	Named and Elected Member of ASCO	American Society of Clinical Oncology
2008	Signed U.S. Constitution	President Pro-Tempore of the United States Senate. Senator Robert C. Byrd
2007	Chief Judge	NIH FARE 2007, Oncology/ Hematology, Tumor Biology, and Chemotherapy, NIH, Bethesda, MD
2007	The Fellows Award for Research Excellence	The National Institutes of Health Bethesda, MD
2006	Certificate of Excellence for Pandemic Flu Preparation	Berkeley County Commission Berkeley, WV
2006	Named and Elected Fellow- F.A.I.C.	The American Institute of Chemists
2005	Outstanding Accomplishments in Research and Medicine Award	Howard University College of Medicine
2005	Medical Grant	American Medical Association Foundation

2009	Invited Speaker	World Cancer Congress, Beijing, China
2009	Distinguished Civilian Faculty Award	GSN/Uniformed services University of the Health Sciences
2008	Named and Elected Member of ASCO	American Society of Clinical Oncology
2008	Signed U.S. Constitution	President Pro-Tempore of the United States Senate. Senator Robert C. Byrd
2007	Chief Judge	NIH FARE 2007, Oncology/ Hematology, Tumor Biology, and Chemotherapy, NIH, Bethesda, MD
2004	Medical Grant	Marcus Family
2003	Travel Grant	The American Society for Pharmacology and Experimental Therapeutics
1998	Honorable Mention in Science	The National Science Foundation
1998	Ford Foundation Pre-Doctoral Fellow Award	The National Research Council
1989	The Combat Medic Achievement Award	Commandant of the U.S. Army Medical Corp.
1989	The Commanders' Award for Leadership	U.S. Army

Education – Non-Degree Granting:)

Year	Degree	Institution/Location/Area of Concentration
May 2006	Certificate	Clinical Research Curriculum The National Institutes of Health Bethesda, MD
Feb 2006	Certificate	Translational Research in Clinical Oncology, The National Cancer Institute, Bethesda, MD
1988	Certificate	Combat Medic Training, Academy of Health Sciences, U.S. Army, Ft. Sam Houston, TX (Valedictorian)

Publications Peer Reviewed:

De Soto JA, The inhibition of breast cancer by Poly(ADP-ribose) polymerase inhibitors. submitted: International Journal of Biological Sciences - Accepted

De Soto JA. Re-evaluating the use of Anthracycline in the treatment of breast cancer in African American Women. J. National Med. Society. - Accepted

De Soto JA. Obesity, breast cancer and bariatric surgery. *J. of Nursing and Bariatric Surgery*. 2008 submitted.

Davis JH, **De Soto JA**, Fryar EB, Southerland WM, Bowen D. Sequential combination chemotherapy in human breast cancer: a basis for increased antineoplastic activity and bone marrow protection. *Cell Mol Biol*. 2007 May 15;53(3):18-26.

De Soto JA, Mandatory HPV vaccination? , *J. Fam. Pract.* 2007 April 56(4):267-268.

De Soto JA, Deng CX, PARP-1 inhibitors, are they the long-sought genetically specific drugs for BRCA1/2-associated breast cancers? *Int. J. Med. Sci.* 2006 Jul: 3:117-23
PMID: 16906222

De Soto JA, Fryar EB, Grissom FE, Southerland WM, Green S, Anti-estrogen cross resistance in human breast cancer. *The Chemist*, 2006 June:83:2-5. ISSN:0009-3025.

Fryar EB, Das JR, Davis JH, **De Soto JA**, Laniyan I, Southerland WM, Bowen D, Raloxifene attenuation of 5-FU/methotrexate cytotoxicity in human breast cancer cells: the importance of sequence in combination chemotherapy. *Anticancer Res*. 2006 May-Jun;26(3A):1861-7. PMID: 16827118

De Soto JA, Wang X, Tominaga Y, Wang RH, Cao L, Qiao W, Li C, Xu, X, Skoumbourdis A, Prindiville SA, Thomas CJ, Deng, CX. The inhibition and treatment of breast cancer with poly(ADP-ribose) polymerase (PARP-1) inhibitors. *Int. J. Biol. Sci.* 2006 2(4):179-185. PMID 16810332

Cao L, Kim S, Xiao C, Wang RH, Coumoul X, Wang X, Li WM, Xu XL, **De Soto JA**, Deng CX, ATM-Chk2-p53 activation prevents tumorigenesis at an expense of organ homeostasis upon Brca1 deficiency. *EMBO J*. 2006 17;25(10):2167-77. PMID 16675955

De Soto JA, Kazi A, Rivera A, Muhammed A, A Case Study: The Treatment of Refractory Schizoaffective Disorder with Aripiprazole. *Pharm Tech*. 2005 21:150-153. ISSN: 8755-1225

De Soto JA, Bowen D, Southerland WM, Hawkins M, The Interaction of the Steroidal Antagonist Faslodex and Methotrexate, *Cell Mol Bio*, 2003 49(7): 1067-9. PMID 14682388

De Soto JA, Bowen D, Davis JH, Sequence Dependent Anti-Estrogen Antagonism between Raloxifene and Methotrexate in Human Breast Cancer Cells, *Anti-Cancer Research*, 2002 , 22(2A): 1007-1009. PMID 12014617

Cronce DT, Famini GR, **De Soto JA**, Wilson LY, , Using Theoretical Descriptors in Quantitative Structure Property Relationships: Some Distribution Equilibria , *Journal of the Chemical Society, Perkins Transactions 2* 1998 44 :1230-7.

Peer Reviewed Proceedings

De Soto JA, The use of Poly(ADP-ribose) polymerase inhibitors in the treatment of cancer, *Proceedings of the World Cancer Congress*, Beijing, China pg 478 June 22-24, 2009.

De Soto JA, Reconsidering Anthracycline Based Chemotherapy in the Treatment of Breast Cancer in African American Women. *Journal of the National Medical Association* 2008 (July 24, 2008).

De Soto JA, The use of (Poly-ADP) Ribose Inhibitors in the Treatment of Breast cancer, *Breast Cancer Research Meeting, Proceedings* June 25, Baltimore. 2009

De Soto JA, Deng CX. The resistance to Taxanes of BRCA2 associated breast cancer. *American Association of Cancer Research*, San Diego CA. April 2008.

De Soto JA, Deng CX, The Enhancement of Paclitaxel Cytotoxicity in Hereditary and Sporadic Breast Cancer by the Poly (ADP) Ribose Polymerase Inhibitor AG14361.

Experimental Biology (FASEB), Proceedings of the Federation of American Societies for Biological Research, Washington, D.C. (April 28, 2007).

De Soto JA, The Inhibition of BRCA-2 Hereditary Breast Cancer with Poly(ADP-ribose) Polymerase (PARP-1) Inhibitors. Proceedings of the National Institutes of Health Research Festival, Bethesda, MD, October 17, 2006.

Tominaga Y, **De Soto JA**, Wang RH, Deng CX, Chemoprevention and therapeutic treatment of BRCA1 associated breast cancer in conditional knockout mice. National AACR Meeting, Washington D.C. April 2, 2006.

De Soto JA, Davis JH, Fryer E, Southerland WM, Bowen D., Anti-Estrogen Cross Resistance in Human Breast Cancer, AACR National Meeting, Anaheim, CA, April 2005.

Davis JH, Fryer E, **De Soto JA**, Bowen D, Utilization of Tamoxifen, Methotrexate and 5-Fluorouracil: A basis for increased anti-Neoplastic activity and Protection of Bone Marrow. FASEB – Experimental Biology. National Meeting, April, San Diego CA. 2003.

De Soto JA, Davis JH, Bowen, Anti-Estrogens Antagonize the Anti-Proliferative Effects of Methotrexate in Human Breast Cancer, FASEB – Experimental Biology. National Meeting The FASEB Journal Abstracts, April, New Orleans LA. 2002 16(4):A176.

De Soto JA, Southerland WH, Hawkins M, Bowen D., Anti-Estrogen Modulation of High Dose Methotrexate Activity in Human Breast Cancer, National Meeting of the Association of Academic Minority Physicians, Journal of the Association of Academic Minority Physicians Proceedings, Washington D.C., Oct 2001 Volume:12(4):154.

De Soto JA, Cronce DT, Famini GR Wilson L. QSAR: The Use of Theoretical Descriptors in Molecular Modeling, American Chemical Society – National Meeting, Anaheim CA, Mar 1995

Invited articles

De Soto JA, Hematomas a common cause of sudden death, 28 Sept, 2009, C1.

De Soto JA, Ear aches – a common ailment of children, 31 Aug 2009, C1-C2.

De Soto JA, Prevent disease: Quit smoking, 6 July 2009, C1-C2.

De Soto JA, Bipolar disorder explained, 8 June 2009, C1-C2.

De Soto JA, What we should know about the swine flu outbreak, 4 May 2009 C1-C2

De Soto JA, Pancreatic cancer the silent killer, 30 Mar 2009, C1-C2

De Soto JA, Thinness is not a sign of success, The Journal 2 Mar 2009 C1-C2

De Soto JA, Hypertension., The Journal 26 Dec 2009. C1-C2.

De Soto JA, Narcissism, the new mental illness? The Journal 29 Dec 2008 C1.

De Soto JA, Treating migraine headaches, The Journal 1 Dec 2008 C1-C2.

De Soto JA, Chemical warfare, The Journal, 3 Nov 2008 C1.

De Soto JA, Today's physician and the Hippocratic Oath, The Journal, 29 Sept 2008 C1-C2.

De Soto JA, Parkinson's disease, The Journal, 25 Aug, 2008 C1.

De Soto JA, Breaking the myths of domestic violence, The Journal, July 28, 2008 C1-C2.

De Soto JA, Underreported disease, The Journal, June 18, 2008 C-2.

De Soto JA, Ovarian cancer is on the rise in West Virginia, The Journal, May 26, 2008 pgs. C1-2.

De Soto JA, Smoking still puts your health at risk, The Journal, April 28, 2008 C-2.

De Soto JA, The signs and symptoms of kidney stone disease, The Journal 1 April 2008. pgs C1-C2

De Soto JA, Understanding inflammatory bowel disease, The Journal 25 Feb 2008. pgs C1-2.

De Soto JA, The facts on Grindler's disease. The Journal 28 Jan 2008. pgs C1-2.

De Soto JA, What is the definition of life? The Journal 31 Dec 2007. pgs C1-2.

De Soto JA, Obesity, BMI and Political Correctness. The Journal 26 Nov 2007. pgs C1-2.

De Soto JA, What you need to know about MRSA? The Journal 29 Oct, 2007. pgs C1-2.

De Soto JA, Should your daughter be vaccinated for HPV? The Journal Sept. 24, 2007. pgs C1-2.

De Soto JA, Know the risks, signs, and symptoms of meningitis. The Journal August 27, 2007. pgs C1-2.

De Soto JA, Lyme disease, what it is and how to prevent it. The Journal, July 30, 2007 pgs C-1.

De Soto JA, Understanding Tuberculosis, The Journal, June 25, 2007, pgs C1-2.

De Soto JA, Malignant Melanoma, The Journal May 28, 2007 pgs C1-2.

De Soto JA, Hippocratic Oath and what it really means, The Journal Apr 23, 2007 pgs C1-2.

De Soto JA, Post-Traumatic Stress Disorder, The Journal, pgs C1-2, April 2, 2007 pgs C1-2

De Soto JA, There may be some good news for MS patients, The Journal, Mar pgs C1-2.

De Soto JA, Sickle cell anemia, The Journal, Feb pgs C-1-2.

De Soto JA, Get tested, colon cancer may be prevented, The Journal, Jan 1, 2007, pgs, C-1-2.

De Soto JA, Facts about HIV, The Journal, Nov 27, 2006, pgs C1-2.

De Soto JA, The future nursing shortage, The Journal Oct 2, 2006, pgs C1-2.

De Soto JA, Prostate hyperplasia, The Journal, Aug. 28, 2006, 2006, pgs C1-2.

De Soto JA, Stem cells can aid in the research of diseases. The Journal, July 31, 2006, pgs C-2-3.

De Soto JA, Breast feed your baby, The Journal, June 22, 2006, pgs C2-3.

De Soto JA, The state of our health care, The Journal, May 30, pgs C2, 2006

De Soto JA, Recognizing and understanding hypothyroidism, The Journal, May 1, 2006, pgs C2.

De Soto JA, Why you should be concerned about the Avian flu, The Journal, Mar 27, 2006, pgs C2-C3.

De Soto JA, Facts, causes, concerns of diabetes, The Journal, Feb 27, 2006, pgs C2-C3

De Soto JA, Breast Cancer: The who's and why's, The Journal, Dec 26, 2005, pgs C2-C3.

De Soto JA, ADHD: Do we really have all the facts? The Journal, Dec 5, 2005, pgs C2-C3.

De Soto JA, Sex and Infertility, The Journal, Oct 31, 2005, pgs C1-2.

Other publications (including web pages)

De Soto JA, HPV Vaccine, http://en.wikipedia.org/wiki/Hpv_vaccine.

De Soto JA, Approaches in Chemo-Hormonal Therapy in the Treatment of Human Breast Cancer: The Modulation of High Dose MTX Cytotoxicity by Anti-Estrogens. Doctoral Dissertation, Advisor: Donnell Bowen Ph.D., Professor of Pharmacology & Oncology. Dec 2005

Media

CNN News, Rob Snyder program, Views of the Presidential Race from West Virginia, October 14, 2008.

The Herald Daily, Speaking out against the strip mining of our mountains, May, 14 2008.

Family Wellness First, Cervical cancer vaccine, Newsletter 030 Jan 11, 2007.

Radio Appearance, WVTS Talk Radio, Will the HPV Vaccine Actually Work?, Jan 12, 2007.

The American Policy Round Table, WV Shouldn't force HPV vaccinations. Jan 23, 2007.

Radio Appearance, WVTS Talk Radio, Is mandating the HPV Vaccine Ethical? Feb 5, 2007.

Television Documentary: The HPV Debate; Cranberry Lodge Productions, Feb 17, 2007.

The Rural Democrat, Bill Watch, Feb 26, 2007.

Honest Human, Standing with those who are standing up, Feb 27, 2007.

Washington Times, CDC opposes law for vaccine, Feb 27, 2007.

Vaccine Autoimmune Project, What is wrong with the vaccine mandate in Illinois?, Mar 5, 2007.

Eagle Forum, HPV mandate stirs protest, Mar 2007.

Planet Chiropractic.com, Risk, informed consent, chiropractic practice, Mar 22, 2007.

International Health News, Vaccinate all 11-12 year old girls against HPV?, Sept, 2007.

Research Activities/Projects/Funding:

Date	Title of Activity/Project/Position (ex. PI, Co PI/Funding Source) /Amount (if applicable)
2008-2013	PI, Uniformed Services University of the Health Sciences, The Treatment of Ovarian, Colon, Pancreatic and Prostate Cancer with Poly-ADP Ribose Polymerase (PARP-1) Inhibitors.
2007-2010	PI, Department of Defense Breast Cancer Research Program, Era of Hope Grant, The Treatment of BRCA1/2 Hereditary Breast Cancer and Sporadic Breast Cancer with Poly(ADP-ribose) PARP-1 Inhibitors and Chemotherapy.
2007-2009	PI, Start Up Grant , USUHS

Consultation Services

Date	Institution/Purpose/Location
2007-2009	Reviewer, International Journal of the Medical Sciences
2007-current	NNMC, Bethesda, MD
2007-current	NIDDK, National Institutes of Health, Bethesda MD
2006-2007	Reviewer, Journal of the National Medical Association
2005-2007	Berkeley County Dept. of Health, Martinsburg WV

Presentations:

National/International

Date	Presentation Title/Sponsor/Location(optional)
June 25, 2009	De Soto JA, The use of Poly(ADP-ribose) polymerase inhibitors in the treatment of cancer, World Cancer Congress, Beijing, China

Feb 10, 2009	De Soto JA, The use of standard chemotherapy with poly(ADP-ribose)polymerase (PARP1) inhibitors in the treatment of hereditary breast cancer. The leading innovation and knowledge sharing meeting, BCRP meeting, Vienna, VA
July 25,2008	De Soto JA, Reconsidering Anthracycline Based Chemotherapy in the Treatment of Breast Cancer in African American Women. National Conference of the National Medical Association, Atlanta Georgia.
June 25, 2008	De Soto JA, The Use of Poly(ADP-ribose) Polymerase Inhibitors in the Treatment of Breast Cancer, Dept. of Defense Breast Cancer Research Meeting –ERA of Hope. Baltimore MD.
Nov. 25, 2006	De Soto JA, The Diagnosis, Treatment and Prognosis of Hereditary and Sporadic Colon Cancer in African Americans. FBCG National Convention, Outstanding Clinician/Researcher, Riverdale, MD
Oct 3, 2005	De Soto JA, Deng C-X, Introducing the use of Poly(ADP-ribose) inhibitors PARP1 in the treatment of human breast cancer. La Sierra University, Combined Chairman's Biological and Chemical Guest Lecturer Series, Riverside, Ca.
July 25, 2005	De Soto JA, The Treatment of Refractory Schizoaffective Disorder with a Novel Dopamine & Serotonin Partial Agonist Aripiprazole. National Conference of the National Medical Association, Philadelphia PA

Local/Regional)

Date	Presentation Title/Sponsor/Location
May 14, 2009	De Soto JA, The use of Poly(ADP-ribose) polymerase inhibitors in the treatment of Ovarian and Breast cancer. USUHS Research Week.
Dec 3, 2008	De Soto JA, Assessing the efficacy of chemotherapy in African breast cancer. Pharmacology research seminar, Howard University College of Medicine.

Nov 17, 2008	De Soto JA, Treatment of Breast Cancer in African American Women, An Afternoon of Research in the Military and Federal Healthcare Systems, USUHS, Bethesda MS
May 14, 2008	De Soto JA, Protecting the Aquifer from Environmental Pollution, Dept. of Environmental Protection WV, Hedgesville.
April 12, 2007	De Soto JA, The Use of Standard Chemotherapy with PARP1 inhibitors in the Treatment of Hereditary Breast Cancer, University of Charleston, Charleston, West Virginia
Oct. 03, 2005	De Soto, JA, Deng C-X, Introducing the Use of Poly (ADP-ribose) inhibitors PARP1 in the treatment of human breast cancer. La Sierra University, Combined Chairman's Biological and Chemical Guest Lecturer Series, Riverside, CA

Teaching Experience:

UNIFORM SERVICES UNIVERSITY OF THE HEALTH SCIENCES

Graduate Courses

Date	Course No.	Topic/Course Level
Spring 2009	GSN 510044	Pharmacology for Advanced Nursing Practice - Coordinator
Spring 2009	PhD 90203-6	Dissertation Seminar – Co-coordinator
Fall2008	GSN 53061	Warfare/Military Readiness Course - Lecturer
Fall 2008	GSN 51055	Pathophysiology for Advanced Nursing Practice - Coordinator
Fall 2008	GSN	Military Readiness - Lecturer

Spring 2007	GSN 51052	Pathology for Advanced Nursing Practice – Co-coordinator
Fall 2007	GSN 51044	Pharmacology for Advanced Nursing Practice – Co-coordinator

Guest Lectures

Date	Course No.	Topic/Course Level (ex. PhD)
Fall 2007	GSN 53061	Therapeutic Intervention in Chemical Warfare/Military Readiness Course

Masters Scholarly Project Guidance

Date	Student	Title/Position
Spring 2008	Watson/Sanchez	Committee Member

Dissertation Guidance

Date	Student	Title/Position
Fall 2009	Maureen Hood	Committee Member

Post-Doctoral Guidance

Date	Post-Doctoral Fellow	Title/Position
2009	Dr. Tatiana Velikovorskaya	Senior Research Associate
2009	Dr. Irina Malyukova	Post-doctoral fellow
2008	Dr. Hyun-Seok Kim	Post-doctoral fellow

Other University Teaching Experience

Date	Course	Role/Institution
Spring 2007	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Spring 2007	Microbiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Spring 2007	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Spring 2007	Anatomy & Physiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Fall 2006	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Fall 2006	Microbiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Fall 2006	Anatomy & Physiology for Nursing Professionals 4 credit	Coordinator Mountain State University
Fall 2006	Anatomy & Physiology lab for Nursing Professionals	Coordinator

	1 credit	Mountain State University
Summer 2006	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Summer 2006	Anatomy & Physiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Summer 2006	Microbiology for Nursing Professionals 4 credits 4 credits	Coordinator Mountain State University
Summer 2006	Microbiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Spring 2006	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Spring 2006	Microbiology lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Spring 2006	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Spring 2006	Anatomy & Physiology lab for Nursing Professionals	Coordinator Mountain State University
Fall 2005	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Fall 2005	Microbiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Fall 2005	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Fall 2005	Anatomy & Physiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University

Summer 2005	Microbiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Summer 2005	Microbiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Summer 2005	Anatomy & Physiology for Nursing Professionals 4 credits	Coordinator Mountain State University
Summer 2005	Anatomy & Physiology Lab for Nursing Professionals 1 credit	Coordinator Mountain State University
Spring 2005	Basic and Clinical Pharmacology 5 units	Instructor Howard University College of Medicine
Spring 2004	Basic and Clinical Pharmacology 5 units	Instructor Howard University College of Medicine

Continuing Ed/Workshops/Seminars:

Date	Title/Organization/Location (City/State)
2009 April	Breast Cancer Update, Bridging the gap between research and patient care Vol 7/ 8 4.25 CME
2009 Mar	Ovarian Cancer Update, bridging the gap between research and patient Care V1/3 3.0 CME
2009 Feb	Visiting Professors Case based discussion on the management of metastatic breast cancer. V1/3 1.5 CME
2009 Jan	Visiting Professors Case based discussion on the management of metastatic breast cancer. V1/2 1.5 CME
2008 Dec	“Breast Cancer Update” Meet the Professors- A case base management for breast cancer in the adjuvant and metastatic setting 2.75 CME
2008 Nov	“Breast Cancer Update”, Meet the Professors Case – A case based

	management of breast cancer in the adjuvant and metastatic setting	2.75 CME
2008 Oct	“Breast Cancer Update/ NSABP” Adjuvant therapy for breast cancer: Where we are, where we are headed.	4.0 CME
2008 Sept	Breast Cancer Symposium, Washington DC	2.5 CME
2008 Aug	“Breast Cancer Update”,Breast Cancer Clinical Case Discussion	2.5 CME
2008 July	“Prostate Cancer Update”, Research to Practice V1/1	4.5 CME
2008 June	American Society of Clinical Oncology National Meeting, Breast Cancer Curricula, Chicago.	10.0 CME
2008 June	“Breast Cancer Update” Research to Practice V7III	4.5 CME
2008 May	“Lung Cancer Update” Research to Practice V5I1	4.5 CME
2008 April	“Ovarian Cancer Update” Research to Practice V1/I1	4.5 CME
2008 Mar	“Colorectal Cancer Update” Research to Practice V7I1	4.5 CME
2008 Feb	“Breast Cancer Update” Research to Practice V7I1	4.5 CME

Academic/Service Activities:

Date	Title (Chair/Member)	Service/Committee
2009	Chair	USUHS Wu – Leonard Awards committee
2008-2009	Chair	Research Policy Committee – Faculty Senate
2008-2009	Member	USUHS Merit Review Committee
2008-2009	Member	USUHS Board of Academic Counselors
2008-2009	Member	CAPT committee working group – Faculty Senate
2008-2009	Member	USUHS Joint Patent, Technology and Research Group
2008-2009	Member	Education committee – Faculty Senate
2008-current	Member	USUHS Faculty Senate
2008-current	Member	Walter Reed Army Institute of Research, Institutional Review Board

		(HURC).
2007-2008	Member	USUHS renovations committee
2007-2008	Member	Faculty Senate- Comparability and faculty welfare committee
2007-2008	Member	Research policy committee – Faculty Senate
2007-current	Member	Ph.D. promotions committee
2007-current	Member	Ph.D. graduate committee

Membership in Professional Organization:

Date	Organization
2008-current	Active Associate Member, American Society for Clinical Oncology
2007-current	Active Member, American Medical Association
2007-current	Active Member, American Association for Cancer Research
2006-current	Member, National Hispanic Medical Association
2005-current	Associate Member, National Medical Association
2005-current	Active Member, American Society for Pharmacology& Exper, Ther.
1996-current	Active Fellow Member, American Institute of Chemist
1995-current	Active Member, American Chemical Society

Other Leadership Activities:

Date	Title/Organization
2008-2009	Chair – Eastern Panhandle Republican Association WV
2008- 2009	Vice-Chair National Ethics Committee AIC
2007 - current	Minority Affairs Consortium, American Medical Association
2006-current	Emergency Services Advisory Council Berkeley County
June 9, 2006-current.	Chief Medical Evaluator - Medical Response and Treatment, Eastern Panhandle Pandemic and Emergency Response Table Top Exercise, Martinsburg WV

Community Activities:

Date	Position/Organization/Location
2008 June 21	Delegate, WV State GOP Convention
2008 Feb 5	Delegate, WV United States Presidential Convention - GOP
2006-current	Humane Society of the United States
2006-2007	Physicians for Peace
2007	Local Emergency Planning Committee
2006-current	The Innocence Project
2005-2006	National Institute of Diabetes, Digestive and Kidney Diseases Institutional Review Board. Ad hoc Member.